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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/590,375	06/09/2000	Keiji Endo	2173-0120P	2206

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/590,375	ENDO ET AL.	
	Examin r	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sh et with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2003; 25 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-10 and 12-27* is/are pending in the application.

4a) Of the above claim(s) *7-9* is/are withdrawn from consideration.

5)☒ Claim(s) *25-27* is/are allowed.

6)☒ Claim(s) *1,3,5,6,10 and 12-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment field February 28, 2003 adding claims 12-14 has been entered.

The amendment field July 25, 2003 canceling claims 2, 4 and 11, amending claims 3, 5, 6 and 13 and adding claims 15-27 has been entered.

Claims 1, 3, 5-10 and 12-27 are pending. Claims 7-9 are withdrawn (see Office action mailed February 25, 2003). Claims 1, 3, 5, 6, 10 and 12-27 are under consideration.

Claim Objections

Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 6 depends from claim 5 that recites as a second mutation "a substitution of a sequence corresponding to the 11th to 100th amino acid residue from the amino terminus set forth in SEQ ID NO:1" (emphasis added), i.e. of a specific sequence corresponding to residues 11-100 of SEQ ID NO:1. However, claim 6 recites as a second mutation "substitution an amino terminal sequence from 1st Asp through 19th Gly of SEQ ID NO:1", i.e. a different sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 6, 10 and 12-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 13, 14 and 17-24 recite a mutant α-amylase comprising an amino acid sequence which is at least 70% homologous to SEQ ID NO:1. While there is support for a parent α-amylase comprising an amino acid sequence which is at least 70% homologous to SEQ ID NO:1 (page 3, lines 9-10, 16-17; page 4, lines 23-25), the examiner is unable to locate adequate support in the specification for 70% homology for a mutant sequence. Thus, there is no indication that mutants having an amino acid sequence which is at least 70% homologous to SEQ ID NO:1 were within the scope of the invention as conceived by Applicants at the time the application was filed.

Claims 3, 5, 6, 10 and 12-24 recite "a [parent] sequence having at lest 95% homology to SEQ ID NO:1". Claims 12, 15, 16 and 17-24 recite "mutant α-amylase comprises an amino acid sequence which is at least 95% homologous to SEQ ID NO:1"

(emphasis added). The specification specifically discloses the invention as a mutant α-amylase obtained by a replacement or deletion "in SEQ ID NO:1 in an α-amylase having said amino acid sequence , or in an α-amylase having homology of at least 70% to said amino acid sequence" (page 3, 1st paragraph). Therefore, the specification provides support for changes in SEQ ID NO:1 or in a sequence that is 70% homologous thereto. Therefore, there is no support for either a parent sequence with 95% homology to SEQ ID NO:1 or a mutant sequence with 95% homology to SEQ ID NO:1.

Claim 5 has been amended to recite "a substitution of a sequence corresponding to the 11th to 100th amino acid residue from the amino terminus set forth in SEQ ID NO:1" (emphasis added). While the specification has support for "replacing an amino acid sequence corresponding to 11 to 100 amino acid residues from the amino terminal (Asp) in the amino acid sequence of SEQ ID NO:1" (page 7, lines 13-16), i.e., replacing residues 1-11, 1-12, 1-13, ... or 1-100, there is no support fie a substitution of specific sequence corresponding to residues 11-100 in SEQ ID NO:1.

Claim 13, with dependent claims 14-24, recites specific properties of a mutant α-amylase. While the specification provides support for specific properties of a parent α-amylase from *Bacillus* sp. KSM-K38 (FERM BP-6946) (SEQ ID NO:1 in this application) or from *Bacillus* sp. KSM-K36 (FERM BP-6945) (SEQ ID NO:4 in this application) (pages 15-17), no properties of mutants of SEQ ID NO:1 other than heat resistance and

resistance to chelating agents have been disclosed in the specification (Examples 5-11). Further more 13(x) reads "is inhibited by 1mM Mn^{2+}" that is shown exclusively for the K38 strain (page 17, lines 23-24).

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 1, 13, 14 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant a-amylase obtained by a specific disclosed substitution at a single position selected from the group consisting of position 11, 16, 49, 84, 144, 167, 169, 178, 188, 190, 205 and 209 in SEQ ID NO:1, specific multiple mutants mutated at positions 167/169, 190/209, 144/190/209, 16/144/190/209, 167/169/190/209, 107/167/169/190/209, 49/107/167/169/190/209, 49/107/205/167/169/190/209 of SEQ ID NO:1, wherein said mutants have increased heat resistance and maintain resistance to chelating agents when compared to SEQ ID NO:1, does not reasonably provide enablement for a mutant of an α-amylase having at least 70% homology thereto with said mutations, wherein said α-amylase mutant either has increased heat resistance and maintain resistance to chelating agents when compared to SEQ ID NO:1 or has the specified properties. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1, 13, 14 and 17-24 are so broad as to encompass any mutant of α-amylase having at least 70% homology to SEQ ID NO:1 in which the amino acid corresponding to the specific positions in SEQ ID NO: 1 are mutated, said mutant a-amylase having increased heat resistance and maintaining resistance to chelating agents. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant α-amylases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the mutants of a single α-amylase having the amino acid sequence of SEQ ID NO:1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to

modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass α-amylase mutants with at least 70% homology to SEQ ID NO:1 in which the amino acid corresponding to specific residues recited in the claims are mutated because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting α-amylase activity; (B) the general tolerance of amylases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any α-amylase residues with an expectation of obtaining any desired α-amylase activity or α-amylase activity combined with increased heat resistance and resistance to chelating agents; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims broadly including amino acid modifications in addition to the specific mutations, said additional mutations comprising about 30% of SEQ ID NO:1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, making a mutant α-amylase having 70% homology to SEQ ID NO:1 and comprising a

specific mutation and having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 16 are confusing as reciting a mutant obtained from a sequence 95% homologous to SEQ ID NO:1, wherein said mutant is 95% homologous to SEQ ID NO:1. Mutations to the sequence will change its homology to SEQ ID NO:1.

Claim 12 is further confusing as reciting "heat resistance which can be improved by combining the mutations" (emphasis added). "can be" refers to a possibility that is not necessarily is implemented. Furthermore, the claim is drawn to a mutant with increased heat resistance compared to SEQ ID NO:1. It is unclear what additional limitation is intended by "can be improved by combining the mutations". Further, it is unclear "improved" compared with what level.

Allowable Subject Matter

Claims 25-27 are allowed.

Response to Arguments

Applicant's arguments filed February 28, 2003 have been fully considered but they are not persuasive.

Applicants argue that "support for"having homology of about 95% to the amino acid sequence of SEQ ID NO:1" is found on page 5, lines 26-27. Support for claims 13 and 14 is found in claim 1, and in the specification on page 16, line 6 to page 17, line 25. No new matter is inserted into the application" (Remarks, page 5). This is unpersuasive for the reasons indicated in the 112, 1st paragraph, new matter rejection above. It is noted while the specification teaches that SEQ ID NO:4 has a homology "of about 95% to the amino acid sequence of SEQ ID NO:1 (page 5, lines 26-27), the claims are not drawn to mutants of SEQ ID NO:1 or SEQ ID NO:4 but to mutants of any sequence with 95% homology to SEQ ID NO:1 which is clearly is not intended by the disclosure as discussed above.

Applicant's arguments filed July 25, 2003 have been fully considered but they are not persuasive.

Applicants argue that "support for a mutant α-amylase comprising an amino acid sequence which is at least 70% homologous to SEQ ID NO:1 is found throughout the specification, such as on page 3, lines 9-10 and 16-17, page 4, lines 23-25, and in abstract" (Remarks, page 10). The examiner disagrees for the reasons discussed above. The above parts of the specification provide support for a parent α-amylase not a mutant α-amylase which is at least 70% homologous to SEQ ID NO:1. Applicants further assert "SEQ ID NO:2 is a liquefying alkaline α-amylase having 66.9% identity to SEQ ID NO:1". It is unclear on what grounds SEQ ID NO:2 that was known in the prior art and is 66.9% homologous to SEQ ID NO:1 obviates the new matter rejection for a mutant α-amylase comprising an amino acid sequence which is at least 70% homologous to SEQ ID NO:1.

Arguments regarding the written description are moot as said rejection is not applied to the current claims.

Applicants assert that "contrary to the Examiner's remarks, the claims do not encompass an unduly broad number of species that are not enabled by the specification" (page 15). This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., α-amylases with increased heat resistance) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the great

number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually numberless possibilities. This would clearly constitute **undue** experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification. As previously stated the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting α-amylase activity; (B) the general tolerance of amylases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any α-amylase residues with an expectation of obtaining any desired α-amylase activity or α-amylase activity combined with increased heat resistance and resistance to chelating agents; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

There are no arguments related to the current 112, 2nd paragraph, rejection of the pending claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

October 17, 2003